carboxylate motif alternating with the ammonium motif. Additional strings and other concerted hydrogen bond motifs are also present. *Crystal data*: $2(C_4H_{10}NO_2^+):(C_2O_4^{2-})$, M_w = 296.28 Daltons; monoclinic, $P2_1/c$; a = 7.4153(9), b = 10.2052(13), c = 9.7584(12) A, β = 108.396(3)°, V = 700.72(15) A^3; Z = 2; T = 298 K; θ_{max} = 26.4°; R_1 = 0.0482 for 939 reflns, $I_o > 2\sigma(I_o)$, ρ_{max} = 0.18 e A^{-3}.

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Keywords: cocrystals, organic phamaceutical, GABA

MS53.P20

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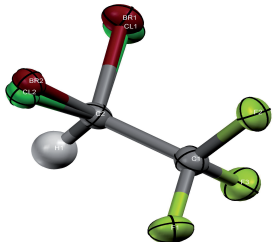
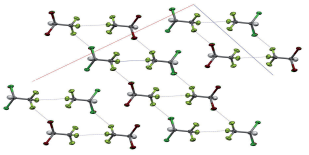
A new polymorph of halothane: An *in-situ* cryo-crystallographic study

Ranganathan Sathishkumar, T.N. Guru Row, *Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore, 560 012, (India).* E-mail: sathishkumar@sscu.iisc.ernet.in

In-situ cryo-crystallographic techniques have been successfully applied to the determination of the crystal structures of compounds which are liquids at room temperature. It has become possible, using this approach to analyze intermolecular interactions of molecular species without the involvement of solvent either as a promoter for crystal growth or as incorporated solvatomorph [1]. 2-bromo-2-chloro-1,1,1-trifluoroethane (Halothane) is a clinically used anesthetic, which has been studied earlier by in situ pressure frozen method using a diamond anvil setup. The crystals were found to belong to triclinic (space group *P*-1) system [2]. The crystals generated in our experiment belong to a monoclinic system (space group *C*2/*c*) with *a* = 18.6626(1) Å, *b* = 4.5759(1) Å, *c* = 12.4030(2) Å, *β* =91.85°, and *V*=1058.59(12) Å^3, thus generates a new polymorphic form. In this structure the bromine and chlorine atoms are substitutionally disordered similar to that found in the in situ pressure frozen polymorph and the occupancies of bromine and chlorine at each site refine to 52:48 ratio. The packing is through several F….F and Cl/Br….F contacts resulting in tetrameric units as shown below.



Halothane structure
(50% Thermal ellipsoid)



Packing shows the tetramer formation in Halothane

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Keywords: cryo-crystallography, polymorphism, disorder

MS53.P21

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Supramolecular chemistry of Anti-HIV nucleoside drugs: Toward smart crystal phases and self-assembled DNA-mimicries

Javier Ellena,[a] Marcio D. Bocelli,[a] Antonio C. Doriguetto,[b] Felipe T. Martins.,[a,c] [a]*Instituto de Física de São Carlos, Universidade de São Paulo – USP, São Carlos, SP, (Brazil).* [b]*Instituto de Ciências Exatas, Universidade Federal de Alfenas – Unifal-MG, Alfenas, MG, (Brazil).* [c]*Instituto de Química, Universidade Federal de Goiás – UFG, Goiânia, GO, (Brazil).* E-mail: javiere@ifsc.usp.br

Multicomponent molecular crystals have been widely screened for several classes of APIs, including the anti-HIV drugs. Lamivudine (β-L-2',3'-dideoxy-3'-thiacytidine, 3TC) and didanosine (2',3'-dideoxyinosine, ddI) are two of the most used NTRIs in anti-HIV therapy. Here, we used a rational strategy to design a $P2_12_12_1$ orthorhombic structure of lamivudine with maleic acid on the basis of lamivudine saccharinate [1]. Likewise, based on the capability of pairing between neutral and protonated lamivudine in the cocrystal of the drug with 3,5-dinitrosalicylate [2], a helical structure in which lamivudine is self-assembled into a DNA-like duplex without phosphodiester linkages was prepared. Crystals of ddI were also prepared using solvothermal techniques and the solid state structure of this drug was solved for the first time.

Chemical aspects of salt formers and crystal assembly features were taken into account for selection of maleic acid in order to assemble into a predicted $P2_12_12_1$ orthorhombic structure with lamivudine. Acid-ionization constant, arrangement of hydrogen bonding functionalities and conformational features were considered for selection of the salt former. A rationally designed crystal preparation and the establishment of structure-property relationships were some advantages of this strategy.

The assembly of the lamivudine double helix structure consists of an interesting example of spontaneous molecular self-organization. Stacking and hydrogen bonding interactions between the cytosine bases of lamivudine were the decisive forces responsible for this structural organization in which alternating neutral and protonated lamivudine conformers are placed into each helical strand. Other contacts such as hydrogen bonds involving duplex-duplex, duplex-anions (chloride and maleate) and duplex-water interactions were also important for the molecular assembly.

Concerning ddI, the pharmaceutical solid state form of the drug has a structure equal to that of the solvothermally prepared ddI crystals described here, while they do not exhibit an identical chemical composition due to different water fraction occupying hydrophobic channels assembled within the crystals. The two crystallographic ddI conformers were in agreement with previous structural elucidation based on solid state NMR techniques [7].

Acknowledgements: FAPESP, FAPEMIG, CAPES, CNPq.

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Keywords: polymorphism, lamivudine, didanosine

MS53.P22

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Probing gels as a media for the growth of co-crystals

Duane Choquesillo-Lazarte, Juan Manuel García-Ruiz, *Laboratorio*

de Estudios Cristalográficos, IACT-CSIC, (Spain). E-mail: duanec@ugr.es

The interest in co-crystals has increased in the last years within the pharmaceutical industry and also the solid-state community due to the possibility of obtaining solid materials with new properties [1]. Co-crystal crystallization strategies, supported by solvent- and solid-based techniques, have also received attention in the search and development of robust methodologies for the screening of co-crystals. This work explores the use of gels in a solvent-based approach to obtain co-crystals. The use of gels as a media permitting diffusive mass transport has been reported for the crystallization of small molecules [2] and proteins [3]. However, most of the gels used for this purpose can only be prepared from aqueous solutions thereby limiting their use to compounds that have been synthesized in aqueous media. Therefore, it is of the utmost importance to find gels that can be prepared from organic solvents and to test their suitability to growth (co-)crystals [4].

A series of co-crystals obtained using model molecules (APIs) and selected co-crystals formers (mainly GRAS carboxylic acids) and grown in water- and/or organic solvent-compatible gels will be presented.

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Keywords: gels, crystallization, co-crystals

MS53.P23

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Structure of Mildronate, its Pharmaceutical Salts and Cocrystals

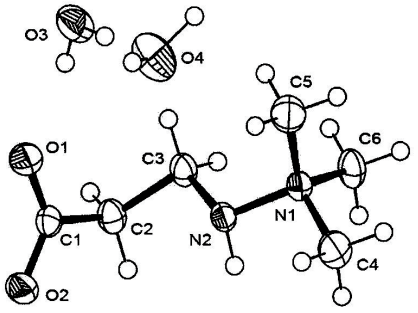
A. Mishnev, I. Kalvins, L. Aleksejeva, A. Lebedev. *Latvian Institute of Organic Synthesis, LV-1006 Riga, (Latvia).* E-mail: mishnevs@osi.lv

Mildronate is a trade mark of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate (meldonium dihydrate) which is an antiischemic and stress protective drug in treating various cardio-vascular diseases and other pathologies involving tissue ischemia [1]. The only shortcoming of the mildronate is its hygroscopicity. It liquefies into syrup after 24 h maintenance at 100% air humidity [2]. Mildronate (in the figure) in crystal adopts zwitterionic, or betaine, form and its hygroscopicity is related to the presence of water channels of 5-7 Å in diameter along **a** axis of the structure.

Search for non-hygroscopic crystalline forms, methods of preparation and physico-chemical properties of meldonium salts were described in [2]. In this work we present crystal structures of meldonium addition salts with phosphoric (in stochiometric ratio 1:1), sulphuric (2:1), boric (1:1), oxalic (1:1) and (2:1), fumaric (2:1) acids and saccharin (1:1). In case of meldonium saccharinate (1:1) two polymorphic forms have been detected. Dependent on the counterion we observed pure salt structures or mixed salt and cocrystal structures. For example in meldonium oxalate (2:1) crystal structure one meldonium molecule has betaine structure while the second one is protonated. In meldonium borate (1:1) structure in the asymmetric unit there are four pairs of meldonium and boric acid molecules. Three meldonium molecules have betaine form and only one is protonated thus forming mixed salt and cocrystal structure. Other structures exhibit pure addition salts.

Meldonium molecule shows considerable conformational flexibility. The values of C1-C2-C3-N2 torsion angle cluster around 72.0° (5 hits) and 177.7° (9 hits) while angle C2-C3-N2-N1 assumes values in the range of 160.1° - 179.9°.

Hygroscopicity test as described in [2] revealed significant water absorption only for meldonium sulphate (2:1). Inspection of its crystal packing showed two structural features which can contribute to water absorbtion. The first is the formation of channels along **a** axis containing sulphuric acid residues and the second is the fact that one oxygen atom of SO_4 residue is not involved in hydrogen bonding and thus is able to interfere with air humidity.



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Keywords: pharmaceutical, salt, cocrystal

MS53.P24

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Aging driven decomposition in Zolpidem hemihydrate

Daniel Vega,[a] Ricardo Baggio,[a] Mariana Roca,[b] Dora Tombari,[b] [a]*Departament Materia Condensada, CAC, Comisión Nacional de Energía Atómica, San Martín, Buenos Aires (Argentina).* [b]*API Division, GADOR S.A., Pilar, Buenos Aires, (Argentina).* E-mail: vega@cnea.gov.ar

Zolpidem is a non benzodiazepine hypnotic drug which effects are similar to those of benzodiazepines by promoting the presence of a particular inhibitory neurotransmitter (gamma-aminobutyric acid, GABA), through the binding to GABA receptors in a similar way and at the same location as benzodiazepines bind. Its usual commercial presentation is in the form of an hemi-tartrate, hydrate, of which several polymorphs are known, the most common of which are usually referred to in the literature as Form A and an alternative Form E. Stable crystallographic forms of different derivatives have also been described in the literature, among them a full tartrate, the free base, a saccharinate, etc. For one of the commercial Forms the crystal structure had been very briefly described, but with no numerical data available as to sustain the description either for checking or comparison purposes. This was the state of the art until recently, when a detailed structural analysis using powder methods reported Form E and two decomposition products [1], identified as the anhydrous 1:1 full tartrate and the free base. The products were derived from a "thermally driven" decomposition process and at the same time that the paper provided valuable structural information on crystalline derivatives of Zolpidem, it threw light onto a very important aspect of Zolpidem hemitartrate thermal decomposition because Form E suffers on heating the same decomposition process as Form A.

While this paper came to light we were engaged in a rather similar project, the structural study of the products generated in an "aging driven" decomposition process of Form A, which ended up to be complementary to the already mentioned "thermally driven" one.

In this work the "aging driven" decomposition of Zolpiden hemitartrate hemihydrate (Form A) was followed by XRPD, and the crystal and molecular structures of the decomposition products studied by single crystal methods. The process is very similar to the "thermally driven" one